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09/478,668	01/06/2000	GARY A. BANNON	HS-102-DIV	1978

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/478,668	Applicant(s) BANNON ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/1/02 has been entered.

2. Claims 37-71 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 37-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a modified peanut protein allergen whose amino acid sequence is identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen, (2) a modified peanut protein allergen whose amino acid sequence is identical to that of an unmodified protein allergen wherein at least one amino acid has been modified in all IgE epitopes of the unmodified peanut protein allergen, (3) the modified peanut protein allergen mentioned above wherein the at least one IgE epitope is one that is recognized when the unmodified peanut allergen is contacted with a pool of sera IgE taken from a group of at least of two individuals that are allergic to the unmodified peanut protein allergen, (4) the modified peanut protein allergen mentioned above wherein at least one modified amino acid is located in the center of the at least one IgE epitope, (5) the modified peanut protein allergen mentioned above wherein at least one IgE epitope of the unmodified protein allergen has been modified by substitution, (6) the modified peanut protein allergen mentioned above wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid, (7) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen

retains the ability to activate T cells, (8) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen retains the ability to bind IgG, (9) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen retains the ability to initiate a Th1-type response, (10) a composition comprising the modified peanut protein allergen whose amino acid sequence is identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18 and IFNγ, (11) the modified peanut protein allergen mentioned above is made in a transgenic plant or animal, (12) the modified peanut protein allergen mentioned above is expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells, (13) the modified peanut protein allergen mentioned above expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells, (14) the modified peanut protein allergen mentioned above wherein the unmodified peanut allergen is obtained from legumes, (15) the modified peanut protein allergen mentioned above made by the process of identifying at least one IgE epitope in an unmodified peanut protein allergen; preparing at least one modified protein allergen whose amino acid sequence is identical to that of an unmodified peanut protein allergen except that at least one amino acid has been modified in at least one IgE epitope; screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified peanut protein allergen, and selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified peanut protein allergen, (16) a modified food allergen whose amino acid whose amino acid sequence is identical to that of an unmodified peanut protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen, (17) the modified food allergen wherein the unmodified food allergen is obtained from a source of legumes, (18) a modified peanut allergen whose amino acid sequence is identical to that of an unmodified peanut allergen except that at least one amino acid has been

modified in at least one IgE epitope so that IgE binding to the modified peanut allege is reduced as compared with IgE binding to the unmodified peanut allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen, (19) the modified peanut allergen mentioned above wherein the unmodified peanut allergen is selected from the group consisting of Ara h1, Ara h2 and Ara h3, (20) the modified peanut allergen wherein the at least one IgE epitope contains at least one amino acid residues that is modified as compared with the unmodified peanut allergen for immunotherapy, **does not** reasonably provide enablement for (1) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen, (2) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one amino acid has been modified in all the IgE epitopes of any unmodified protein allergen, (3) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one IgE epitope is one that is recognized when the unmodified protein is contacted with a pool of sera IgE taken from a group of at least of two individuals that are allergic to the unmodified peanut protein allergen, (4) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one modified amino acid is located in the center of the at least one IgE epitope, (5) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one IgE epitope of the unmodified protein allergen has been modified by substitution, (6) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one hydrophobic amino acid in the at least one IgE epitope of any unmodified protein allergen has been substituted by any neutral or any hydrophobic amino acid, (7) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains the ability to activate T cells, (8) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains

the ability to bind IgG, (9) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains the ability to initiate a Th1-type response, (10) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen is *any* portion of *any* unmodified protein allergen, (11) a composition comprising *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and *any* "immune stimulatory sequences", (12) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen wherein the modified protein allergen is made in a transgenic plant or animal, (13) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein expressed in a recombinant host such as plants, and animals, bacteria, yeast, fungi, and insect cells, (14) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein wherein the unmodified protein allergen is *any* milks, *any* grains, *any* eggs, *any* fish, *any* crustaceans, *any* mollusks, *any* insects, *any* molds, *any* dust, *any* grasses, *any* trees, *any* weeds, *any* mammals, *any* natural latexes, (15) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is

reduced as compared with IgE binding to *any* unmodified protein made by the process of: identifying at least one IgE epitope in an unmodified peanut protein allergen; preparing at least one modified protein allergen whose amino acid sequence is identical to that of an unmodified peanut protein allergen except that at least one amino acid has been modified in at least one IgE epitope; screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified peanut protein allergen, and selecting a modified protein allergen with decreased binding to IgE as compared to *any* unmodified peanut protein allergen, (16) *any* combination of *any* natural protein allergen and *any* masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of *any* natural protein allergen in such a way that IgE binding is reduced as compared with IgE binding to *any* "natural" protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to any natural protein allergen, (17) *any* combination of *any* natural protein allergen and *any* masking compound, mentioned above wherein the at least one IgE epitope is one that is recognized when any natural protein is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to *any* natural protein allergen, (18) *any* combination of *any* natural protein allergen and *any* masking compound wherein the combination retains the ability to activate T cells, bind IgG, or initiate a Th1-type response, (19) *any* modified food allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified food allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen, (20) *any* modified food allergen mentioned above is obtained from *any* milks, *any* grains, *any* eggs, *any* fish, *any* crustaceans, and *any* mollusks, (21) *any* modified food allergen mentioned above is obtained from wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, (23) *any* modified protein or food allergen mentioned above wherein the least one IgE epitope contains *any* 1-6, *any* 1-5, *any* 1-4, *any* 1-3, or *any* 1-2 amino acid residues that are modified as compared with *any* unmodified protein or food allergen for use in immunotherapy, vaccine, and to genetically engineer organisms such as plants and animals to produce proteins with less

likelihood of eliciting an IgE response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only modified food allergens from peanut consisting of IgE binding epitopes from Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

Besides the specific modified food allergen such as peanut Ara h1, Ara h2, Ara h3 allergens consisting of the specific SEQ ID NO mentioned above, there is insufficient guidance as how to make and use *any* modified protein allergen such as any legumes, milks, grains, eggs, fish, crustaceans, mollusks, and any modified food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen. The specification does not define the term "substantially". Further, there is insufficient working examples demonstrating that any modified

protein or food allergen after modification by substitution, deletion, addition would retain the ability to activate T cells, bind IgG and initiate a Th-1 type response, much less bind IgE for treating any allergy. The specification fails to provide *any* guidance and working examples as how to make and use any combination of *any* "natural protein allergen" and *any* masking compound being covalently or non-covalently bound to at least one IgE epitope of any natural protein allergen. The specification fails to provide guidance as to where are all the IgE epitopes within the full-length sequence of any protein allergen and any food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, weeds, trees, mammals, and natural latexes. Even if the IgE epitope has been identified, there is no working examples demonstrating any modified protein allergen or food allergen, or *any* "portion" of said unmodified protein would retain the structure and function, much less activate T cells, bind IgG and initiate a Th-1 type response, in turn, would be useful for immunotherapy.

There is no recognition in the art that sequence identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Fasler *et al.* (of record, PTO 892) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record, PTO 1449) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (of record, PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while

substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* (of record, PTO 892) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* (of record, PTO 892) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Given the indefinite number of undisclosed modified protein allergen, and food allergen, it is unpredictable which undisclosed modified protein allergen and food allergen would be useful for immunotherapy. Since *any* modified protein or food allergen and *any* masking compound are not enabled, it follows that any combination thereof is not enabled. Even if the specific peanut food allergen is recited in claims 63-64, only the specific amino acid substitution within specific amino acid residue within the full length of SEQ ID NO: 1 and 2 such as the ones disclosed on page 24, line lines 16-24 has reduced IgE binding less than 1% of that observed to the unmodified allergen.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 37 and dependent claims therefrom have been amended, and claims 54-59 have been canceled. (2) The specification exemplification of modified peanut allergens and the teachings are applicable to other unmodified protein allergens.

However, the amended claims still recite *any* modified protein allergen and *any* modified food allergen. Claims 54-59 are still pending. Although the claimed method may be applicable to other protein allergen, the instant claims are drawn to a product. Besides the specific modified food allergen such as peanut Ara h1, Ara h2, Ara h3 allergens mentioned above, there is insufficient guidance as how to make and use *any* modified protein allergen, and any modified food allergen whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen. The specification does not define the term "substantially". Further, there is insufficient working examples demonstrating that any modified protein or food allergen after modification by substitution, deletion, addition would retain the ability to activate T cells, bind IgG and initiate a Th-1 type response, in turn, useful for treating any allergy. The specification also fails to provide *any* guidance and working examples as how to make and use any combination of *any* "natural protein allergen" and *any* masking compound being covalently or non-covalently bound to at least one IgE epitope of any natural protein allergen. The specification fails to provide guidance as to where are all the IgE epitopes within the full-length sequence of any protein allergen and any food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, weeds, trees, mammals, and natural latexes. Even if the IgE epitope has been identified, there is no working examples demonstrating any modification of any IgE epitope of *any* protein allergen, *any* food allergen, *any* "portion" of *any* unmodified protein or food allergen would retain the structure and have similar function such as activate T cells, bind IgG and initiate a Th-1 type response, in turn, would be useful for immunotherapy.

5. Claims 37-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the

unmodified peanut protein allergen, (2) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one amino acid has been modified in all the IgE epitopes of any unmodified protein allergen, (3) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one IgE epitope is one that is recognized when the unmodified protein is contacted with a pool of sera IgE taken from a group of at least of two individuals that are allergic to the unmodified peanut protein allergen, (4) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one modified amino acid is located in the center of the at least one IgE epitope, (5) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one IgE epitope of the unmodified protein allergen has been modified by substitution, (6) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein at least one hydrophobic amino acid in the at least one IgE epitope of any unmodified protein allergen has been substituted by any neutral or any hydrophobic amino acid, (7) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains the ability to activate T cells, (8) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains the ability to bind IgG, (9) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen retains the ability to initiate a Th1-type response, (10) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen wherein the modified protein allergen is *any* portion of *any* unmodified protein allergen, (11) a composition comprising *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and *any* "immune stimulatory sequences", (12) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of

any unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen wherein the modified protein allergen is made in a transgenic plant or animal, (13) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein expressed in a recombinant host such as plants, and animals, bacteria, yeast, fungi, and insect cells, (14) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein wherein the unmodified protein allergen is *any* milks, *any* grains, *any* eggs, *any* fish, *any* crustaceans, *any* mollusks, *any* insects, *any* molds, *any* dust, *any* grasses, *any* trees, *any* weeds, *any* mammals, *any* natural latexes, (15) *any* modified protein allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein made by the process of: identifying at least one IgE epitope in an unmodified peanut protein allergen; preparing at least one modified protein allergen whose amino acid sequence is identical to that of an unmodified peanut protein allergen except that at least one amino acid has been modified in at least one IgE epitope; screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified peanut protein allergen, and selecting a modified protein allergen with decreased binding to IgE as compared to *any* unmodified peanut protein allergen, (16) *any* combination of *any* natural protein allergen and *any* masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of *any* natural protein allergen in such a way that IgE binding is reduced as compared with IgE binding to *any* "natural" protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE

taken from an individual that is allergic to any natural protein allergen, (17) *any* combination of *any* natural protein allergen and *any* masking compound, mentioned above wherein the at least one IgE epitope is one that is recognized when any natural protein is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to *any* natural protein allergen, (18) *any* combination of *any* natural protein allergen and *any* masking compound wherein the combination retains the ability to activate T cells, bind IgG, or initiate a Th1-type response, (19) *any* modified food allergen whose amino acid sequence is "substantially" identical to that of *any* unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to *any* modified food allergen is reduced as compared with IgE binding to *any* unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen, (20) *any* modified food allergen mentioned above is obtained from *any* milks, *any* grains, *any* eggs, *any* fish, *any* crustaceans, and *any* mollusks, (21) *any* modified food allergen mentioned above is obtained from wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, (23) *any* modified protein or food allergen mentioned above wherein the least one IgE epitope contains *any* 1-6, *any* 1-5, *any* 1-4, *any* 1-3, or *any* 1-2 amino acid residues that are modified as compared with *any* unmodified protein or food allergen for use in immunotherapy, vaccine, and to genetically engineer organisms such as plants and animals to produce proteins with less likelihood of eliciting an IgE response.

The specification discloses only modified food allergens from peanut consisting of IgE binding epitopes from Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated

thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of modified allergens from peanut mentioned above, there is insufficient written description about the structure associated with functions of *any* modified protein allergen *any* food allergen, and *any* combination of *any* modified protein allergen. Even if the specific peanut food allergen is recited in claims 63-64, only the specific amino acid substitution within specific amino acid residue within the full length of SEQ ID NO: 1 and 2 such as the ones disclosed on page 24, line lines 16-24 has reduced IgE binding less than 1% of that observed to the unmodified allergen. The specification disclosed only one species of modified food allergen from peanut, given the lack of a written description of any additional species of modified protein allergen, modified food allergen and combination thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 37 recites a modified protein allergen whose amino acid sequence is (a) "substantially" identical to that of *any* unmodified protein allergen except that (b) at least one amino acid has been modified in at least one IgE epitope so that (3) IgE binding to *any* modified protein allergen is reduced as compared with IgE binding to *any* unmodified protein; (2) the specification provides references to a list of known amino acid sequences of a variety of unmodified protein allergen and (3) the inventive principles apply to other unmodified protein allergens.

However, the amended claims still recite any modified protein allergen and any food allergen. The specification discloses only modified food allergens from peanut consisting of IgE binding epitopes from Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). With the exception of the specific modified food allergens from peanut mentioned above, there is insufficient written

description about the structure associated with functions of *any* modified protein allergen, any food allergen and *any* combination of *any* modified protein allergen thereof. With regard to the list of known unmodified protein allergen, the list is merely an invitation for further experimentation.

6. Claims 54-59 and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 54-59 and 65-69 as written represent a departure from the specification and the claims as originally filed.

The recitation of "In combination, a natural protein allergen and a masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen is such as a way that IgE binding is reduced as compared to the natural protein allergen in the absence of the masking compound wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen" is not support by the specification or by the claims as originally filed.

The recitation of "the masking compound is an antibody that binds non-covalently to the at least one IgE epitope" in claim 56 is not support by the specification or by the claims as originally filed.

The recitation of "1-6 amino acid residues" in claim 65 has no support in the specification and the claims as originally filed.

The recitation of "1-5 amino acid residues" in claim 66 has no support in the specification and the claims as originally filed.

The recitation of "1-4 amino acid residues" in claim 67 has no support in the specification and the claims as originally filed.

The recitation of "1-3 amino acid residues" in claim 68 has no support in the specification and the claims as originally filed.

The recitation of "1-2 amino acid residues" in claim 69 has no support in the specification and the claims as originally filed. Applicants have not pointed out the support for said "1-6, 1-5, 1-4, 1-3 and 1-2 amino acid residues".

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 54-59 have been canceled.

However, claims 52 and 54-59 are still pending.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 37-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially" in claims 37, 60 and 63 is ambiguous and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention because the specification does not define the term "substantially".

The recitation of "In combination" in claims 54-59 is improper. It is suggested that the claims be recite a composition comprising.

The recitation of "in such as way" in claim 54 is indefinite and ambiguous because it is not clear which way applicants intend to claim. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The recitation of "protein allergen" in claim 61 has no antecedent in basis in base claim 60. Base claim 60 requires "a modified food allergen".

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that claim 37 and dependent therefrom have been amended and claims 54-59 have been canceled.

However, claims 52 and 54-59 are still pending.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 37-39, 41-46, 48-51 and 53 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,547,669 (Aug 1996, PTO 892).

The '669 patent teaches a modified protein allergen such as FEL DI from the cat which is a mammal, whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that modified protein binding to IgE is reduced (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The reference modified protein allergen is expressed recombinantly in host cell such as bacteria (E coli), and the reference modified protein allergen stimulates T cell activity such as T cell proliferation better than unmodified protein allergen (See column 24, lines 8-67, bridging column 25, lines 1-32, in particular), initiates delayed type sensitivity which is Th-1 response (See column 26, lines 60-62, in particular) and reduces IgE binding (See column 22, lines 44, column 23, lines 59-61, in particular). Claims 48-49 are included in this rejection because the claims recite a product by process. The recitation of a process limitation in claim 48-49 is not seen as further limiting the claimed product, since multiple processes can make equivalent products. While the reference is silence that the reference modified protein allergen has the property of that recited in claim 44, the ability to bind IgG is the inherent property of the reference modified protein allergen. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the antibodies of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '669 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 37 has been amended, (2) the '669 patent teaches the generation of wholly artificial polypeptides whose amino acid sequence differs substantially

from that of any natural protein antigen, (3) the '669 patent teaches a recombitope or a modified recombitope peptide that would have an amino acid sequence that is substantially identical to that of an unmodified protein allergen.

However, the '669 patent teaches a "modified" protein allergen such as FEL DI from the cat which is a mammal, whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that modified protein binding to IgE is reduced (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). Further, the amended claims still recite any modified protein allergen and the position of the modified amino acid residue within the full length of an unmodified protein allergen is not specified. Since the reference-modified protein has all the functional properties such as reduce IgE binding, activates T cell proliferation of the claimed invention, the modified amino acid is inherently within the IgE epitope of the unmodified protein allergen.

11. Claims 54-59 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,449,669 (Sept 1995, PTO 892).

The 5,449,669 patent teaches a combination of synthetic polypeptide based on the natural protein allergen such as shrimp tropomyosin Pen i I and a masking compound such as tropomyosin-specific IgE antibody being non-covalently bound to at least one of the IgE epitope of the native protein tropomyosin using sera of allergic patients and determining the inhibition of binding of tropomyosin-specific IgE antibodies to tropomyosin (See column 6, lines 32-68, column 7, lines 1-16, in particular). Claims 57-59 are included in this rejection because since the claimed protein allergen is a natural protein allergen, it is inherent that the natural protein has the ability to activate T cells, binds IgG and initiates a Th1-type response. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 54-59 have been canceled. However, claims 54-59 are still pending.

12. The filing date of the instant claims 52 and 64-69, is deemed to be the filing date of the priority application 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998, as USSN 08/717,933 filed Sept 23, 1996 do not support the claimed limitations of "Ara h3, " in claims 52 and 64, "1-6 amino acid residues" in claim 65, 1-5 amino acid residues" in claim 66, 1-4 amino acid residues" in claim 67, 1-3 amino acid residues" in claim 68, 1-2 amino acid residues" in claim 69. Applicants are reminded that such priority for the instant limitations requires a written description and enablement under 35 U.S.C. § 112, first paragraph.

13. Claims 37, 52, 60-61 and 63-71 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449; see entire document).

Burks *et al* teach a modified protein allergen such peanut (food) allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified food allergens such as peanut Ara h1 except that one amino acid has been modified in one of the IgE epitope so that IgE binding to the reference modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen, and the reference IgE epitope is recognized by 15 individuals who is allergic to the unmodified peanut allergen (See entire document, Materials and Methods, Fig 6, in particular). The reference modified protein allergen is based on a protein obtained from legumes, which peanut is part of the family. The reference modified protein allergen whose immunodominant IgE epitope of unmodified Ara h1 protein or portion thereof can be mutated to non-IgE binding epitopes by a single amino acid changes (See Fig. 6-7, in particular). The modified reference allergen is mutated in the center of one or more IgE binding epitopes by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, in particular). The modified allergen is made by the process of identifying one or more IgE binding sites in an allergen, mutating one or more amino acid in an IgE binding site, screening for IgE binding to the mutated allergen and selecting the modified allergens with the least binding to IgE (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular). The reference further teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). Burks *et al* teach it is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic homologue in the peanut genome to develop a hypoallergenic peanut and for making and using

hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Claims 65-69 are included in this rejection because the reference teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular) and mutates at least one amino acid in the IgE in an IgE binding site (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular) to develop a hypoallergenic peanut for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). The reference modified-allergen has reduced IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 37 and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Hoyne *et al* (of record, Immunology and Cell Biology 74: 180-186, 1996, PTO 892).

The teachings of the '669 patent have been discussed supra.

The claimed invention in claim 47differs from the reference only by the recitation of in combination of the modified allergen and an adjuvant selected from the group consisting of IL-12, and IFNγ.

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering modified allergen peptide in the presence of IL-12 or IFNγ (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate modified allergen in the presence of IL-12 or IFNγ because the key to a successful peptide-based immunotherapy depends on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ because IL-12 or IFNγ would down-regulate ongoing Th2 responses in vivo by suppressing IgE production as taught by Hoyne et al (See page 183, column 2, in particular).

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) neither the secondary reference is cited for or provides any teachings or suggestion that could overcome the deficiency in the '669 patent.

However, the amended claims still recite *any* modified protein allergen and the position of the modified amino acid residues within the full length of an unmodified protein allergen is not specified. the '669 patent teaches a modified protein allergen such as FEL DI from the cat which is a mammal, whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that modified protein binding to IgE is reduced (See column 3, lines 36-

45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). Since the reference modified-protein allergen has all the functional properties such as reduce IgE binding, activates T cell proliferation of the claimed invention, the modified amino acid residue is inherently within the IgE epitope of the unmodified protein allergen.

17. Claims 37 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Burks *et al* (of record, J Allergy Clin Immunol 6-93(4): 743-50; 1994 PTO 1449).

The teachings of the '669 patent have been discussed supra.

The claimed invention in claim 52 differs from the reference only by the recitation that the modified protein allergen is peanut protein selected from the group consisting of Ara h1, Ara h2 and Ara h3.

Burks *et al* teach a major allergen of peanuts such as Ara h1 and the IgE binding specificity of Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). Burks et al further teach that the allergen is purified by affinity column chromatography and the Ara I allergen has a molecular weight of 63.5 kd and an isoelectric point of 4.55 while the second allergen such as Ara II has a molecule weight of 17 kd and an isoelectric point of 5.2(See Abstract, page 749, column 1, first full paragraph, in particular). The reference further teaches that peanuts are considered one of the most allergenic food (See page 743, column 1, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify at least one of the IgE binding epitope of Ara h1 or Ara h2 as taught by Burks by amino acid substitution as taught by '669 patent for a modified protein allergen wherein the IgE binding of the modified protein allergen is reduced for desensitization immune therapy. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Burks *et al* teach peanuts are considered one of the most allergenic food (See page 743, column 1, in particular) the IgE binding specificity of one of the major protein allergen of peanut Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). The '699 patent teaches that the modified the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular).

Applicants' arguments filed 7/1/02 have been fully considered but are not found persuasive.

Applicants' position is that claim 37 has been amended and claim 52 has been canceled.

However, the amended claim still recites *any* modified protein allergen. Claim 52 is still pending.

18. Claims 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) or Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449; see entire document) each in view of US Pat No. 5,449,669 (Sept 1995, PTO 892).

The teachings of the 5,547,669 patent and Burks *et al* have been discussed supra.

The claimed invention in claim 61 differs only by the recitation that the unmodified protein allergen is obtained from crustacean.

The claimed invention in claim 62 differs only by the recitation that the unmodified protein allergen is obtained from shrimp.

The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify at least one of the IgE binding epitopes of shrimp as taught by the 5,449,669 patent using the method as taught by the 5,547,669 patent or Burks *et al* for a modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified protein allergen as taught by the 5,547,669 patent and Burks *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the 5,449,669 patent teaches IgE epitopes are useful in diagnosis and/or treatment of allergies. The 5,547,669 patent the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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